REMARKS

Status of the claims

With entry of the amendment, claims 44-82 are pending. Claim 68 was rejected under 35 USC 112, second paragraph as being indefinite; claims 44-47, 49-52, 54, and 58-74 were rejected under 35 USC 102(b) as being anticipated by Smith et al. (WO 98/31840; and claims 42-52, 54, 55, and 58-68 were rejected under 35 USC 103(a) as being unpatentable over Kleiber et al. (WO 96/41811), in view of Huber et al. (Nucleic Acids Res. 21:1061-1066) as evidenced by Vogelstein et al. (1979 PNAS 76:615-619). The Examiner did not consider claims 56 and 57. However, because claims 56 and 57 are directed to a species of generic claim 55, which Applicants submit is allowable, claims 56 and 57 should be rejoined. Claims 75-82 are newly added.

In light of the amendments above and remarks below, Applicants respectfully request allowance of the claims.

Amendments to the claims

Applicants have amended the claims as shown above and explained below. Each amendment is fully supported by the application as originally filed, and introduces no new matter.

Claim 44 has been amended to clarify that the method involves selecting a defined amount of DNA to be isolated from the samples and choosing a discrete amount of a silica-containing solid support necessary to isolate the defined amount of DNA. Support for the amendment can be found at least at p. 8, lines 23-26, Example 1, p. 24-p. 25; Example 2, p. 25-p. 26, and Example 7, p. 32-p. 33.

Claims 47-49 have been amended to depend from claim 46 instead of claim 45 to correct the dependency to provide antecedent basis for silica magnetic particles.

Claims 56 and 57, which depend from claim 55, are amended to clarify that the sample comprises a solid support that is paper (claim 56) or a swab (claim 57). Support for the amendments can be found at least in original claim 13 and at page 7, line 11 of the specification.

Claim 58 is amended to depend from claim 44 and to clarify that the sample is a forensic sample. Support for the amendment can be found at least at p. 1, lines 27-29.

Claims 61 and 65 are amended to correct typographical errors.

Claim 66, which depended from claim 44, has been rewritten in independent form to include the limitation of claim 44, prior to amendment of claim 44. It is also further includes an elution step and is amended for purposes of clarity to reflect that the DNA isolated by the method is suitable for use in a molecular biological procedure. Support for the amendment is found at least in claim 44, claim 66, p. 22, line 30-p. 23, line 10, and at p. 6, lines 21-23.

Claim 67 is amended for purposes of clarity in light of the amendment to claim 66.

Claim 68 is amended to clarify that the CODIS loci are the Combined DNA Index System loci. Support for the amendment can be found at least at page 2, lines 6 and 7.

Claim 69 is amended to clarify that the kit comprises silica magnetic particles that are used in a discrete amount to bind a defined amount of DNA from each sample.

Support for new claim 75 can be found at least at p. 23, lines 21-22.

Support for new claim 76 can be found at least at 22, lines 30-32.

Support for new claim 77 can be found at least at p. 23, lines 5-6, Example 2.

Support for new claim 78 can be found at least at p. 22, lines 32-33.

Support for new claim 79 can be found at least at p. 22, lines 32-33.

Support for new claim 80 can be found at least at p. 6, lines 4-9; p. 7, lines 2-4; Example 2.

Support for new claim 81 can be found at least at p. 25, lines 33-39; p. 7, lines 2-4.

Support for new claim 82 can be found at least at Example 10, p. 39 Table 13-p. 14, line 5.

Species Election

In the Office Action of July 31, 2007, the Examiner referred to a July 11, 2007 telephone exchange in which the Examiner informed the undersigned that, in his opinion, a paper sample or swab sample did not fall within the scope of Applicants' elected species of solid support (i.e., a forensic sample).

Applicants have amended claim 58, which depended from claim 55, to depend from claim 44 and to clarify that the sample of claim 44 is a forensic sample. Claim 55 requires that the sample of claim 44 comprise a solid support. Claims 56 and 57 depend from claim 55 and are directed to paper and a swab, respectively. Claims 56 and 57 have been amended to clarify that the sample of claim 55 comprises paper or a swab.

Applicants respectfully submit that a forensic sample may include liquids or solids, and that paper or a swab may be a forensic sample. Further, Applicants submit that the generic claims are allowable and, accordingly, request that all claims directed to species of the generic claim be rejoined and allowed.

Examiner interview

In an October 15, 2007 in person interview, Dr. Rex Bitner, an inventor of claims of the instant application, and the undersigned discussed the invention with Examiners Christopher Gross and Jon Epperson. Applicants wish to thank the Examiners for the courtesy of their time and attention to this application.

The Examiners indicated that the rejection of claims as being anticipated by Smith et al. (WO 98/31840) was made in error and that the rejection would be withdrawn. In addressing the rejection under 35 USC 103(a), Dr. Bitner described the invention and explained how Applicants' approach to isolating DNA represents a departure from prior art methods. The Examiners acknowledged that the prior art of record provides no motivation to make Applicants' methods, as disclosed in the application and as explained by Dr. Bitner. However, the Examiners suggested that clarifying amendments to better define the invention may be indicated. Also discussed was the widespread enthusiasm among those who work in the field of DNA isolation for Applicants' methods, which underscores the nonobviousness of Applicants' methods. The Examiners indicated that a declaration submitting evidence of secondary indicia of non-obviousness would be favorably considered.

Priority

The Examiner stated that the instant application is not entitled to receive the benefit of the priority claim to US Serial No. 08/785,097 (the '097 Application) because that application does not disclose isolating a consistent amount of DNA from each sample. Applicants acknowledge that the invention as claimed was not disclosed in the '097 Application.

Rejections under 35 USC 112, second paragraph

Claim 68 was rejected under 35 USC 112, second paragraph as being indefinite for the recitation of "CODIS", which the Examiner asserts is unclear because it could allegedly refer to choriodecidual inflammatory syndrome or the Federal Bureau of Investigation's Combined DNA

Index System. Applicants respectfully submit that, when taken in the context of the rest of the claim, and as defined in the specification, one of skill in the art would understand that "CODIS" loci refers to Combined DNA Index System loci. Nevertheless, Applicants have amended claim 68 to clarify that the recited loci are the Combined DNA Index System loci.

Rejections under 35 USC 102(b)

Claim 44-47, 49-52, 54, 55, and 58-74 are rejected under 35 USC 102(b) as being anticipated by Smith et al. (WO 98/31840). Applicants note that WO 98/31840 is a published PCT application that claims priority and is identical to the '097 Application, which the Examiner indicated does not provide support for the claims (see above). In view of the fact that the '097 Application does not provide support for the claims, the WO 98/31840 cannot and does not anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejection be withdrawn.

Rejections under 35 USC 103(a)

Claims 44-52, 54, 55, and 58-68 are rejected under 35 USC 103(a) as being unpatentable over Kleiber et al. (WO 96/41811), in view of Huber et al. (Nucleic Acids Res. 21:1061-1066) as evidenced by Vogelstein et al. (1979 PNAS 76:615-619).

Kleiber is characterized as teaching porous and poreless boro/alumino/zirconio-silicate magnetic particles useful for DNA isolation. Further, Fig. 1 of Kleiber is cited as teaching contacting each sample with a discrete amount of a silica-containing solid support under conditions that allow reversible binding of the defined amount of DNA to the solid support. Fig. 2 of Kleiber et al., which presents the results of an experiment described in Example 3 of Kleiber et al., is cited as teaching separating DNA from the support to isolate a defined and consistent amount of DNA from each sample. The Examiner acknowledged that Kleiber et al. fails to teach that each sample comprises DNA in excess of the binding capacity of the particles.

Huber et al. is cited as teaching high resolution liquid chromatography of DNA fragments on poly(styrene-divinylbenzene) (PS-DVB) particles. Citing to Fig. 9 and p. 1066, third paragraph of Huber et al., the Examiner characterized Huber et al. as teaching that up to five μg of DNA was loaded on to a PS-DVB column having a capacity of 0.5 μg. Thus, the Examiner concluded that it would have been obvious to measure the DNA binding capacity of the particles of Kleiber et al. using the method reported by Huber et al. The Examiner asserts that one of skill

in the art would be motivated to do so in order to determine the upper limit of DNA binding to the particles of Kleiber et al.

Vogelstein is cited as teaching the general principle that different types of silica containing material have different binding capacities.

Applicants respectfully submit that the Office action has failed to establish that claims 44-52 and 54-68 are prima facie obvious over the cited art.

Applicants note that Fig. 1 of Kleiber et al. is an illustration of method in which DNA is isolated from a single sample. Nothing in Fig. 1 or in the description of Fig. 1 indicates that the illustrated method was directed to isolating a defined amount of DNA from a sample, let alone defined and consistent amounts from multiple samples, as the preamble and steps of the instantly claimed invention requires. As one of skill in the art would appreciate, Fig. 1 appears to illustrate quantitative recovery of the DNA present in the sample (six of six DNA molecules are bound and eluted), as opposed to recovery of a defined amount of DNA that is dependent on the binding capacity of a silica containing solid support and independent of the amount of DNA in the sample. In fact, the focus of Kleiber is on using glass magnetic particles to obtain high yields (Please see p. 12, where Kleiber states that using the particles of the invention, the yield of biological materials is relatively high; Bitner declaration, paragraph 6).

As the Examiner has acknowledged, Kleiber does not teach a method of isolating a defined and consistent amount of DNA from multiple samples in which each sample comprises DNA in excess of the binding capacity of the discrete amount of silica-containing solid support in order to obtain a defined and consistent amount of DNA. To the contrary, as described in Example 3 of Kleiber, which corresponds to the results presented in Fig. 2 cited as teaching isolating consistent amounts of DNA, Kleiber bound DNA from each of multiple identical samples to three different preparations of glass magnetic particles (GMP 2-4). The experiment described in Example 3 was designed to control for all variables that affect DNA yield other than particle preparation, by treating identical samples identically. One of skill in the art would understand that the purpose of Example 3 was to evaluate similarities or differences between three different preparations of glass magnetic particles. Thus, Kleiber does not teach the problem of isolating defined and consistent amounts of DNA from multiple samples, nor does Kleiber provide the solution of the instantly claimed invention (i.e., selecting a defined amount of DNA to be isolated, choosing a discrete amount of a silica-containing solid support necessary

to isolate the defined amount of DNA from each sample, and contacting each sample with the discrete amount of a silica-containing solid support, each sample comprising DNA in excess of the binding capacity of the discrete amount of silica-containing solid support, under conditions that allow reversible binding of the defined amount of DNA to the solid support).

Huber et al., which is directed to separating DNA fragments of different sizes (e.g., DNA restriction fragments and PCR products) according to size using high-performance liquid chromatography on alkylated non-porous poly(styrene-divinylbenzene) particles. Separation occurs as a result of differential retention on the column based on chain length. The method is described as effecting separation of relatively small DNA fragments differing in chain length by 1-5% up to a size of 500 base pairs.

Huber et al. does not cure the deficiencies of the primary reference. Fig. 9 of Huber et al. shows that the peak half-width increases when the column is overloaded, which reflects increased retention time and decreased resolution. Because the goal of the methods described in Huber et al. is to increase resolution in separation of DNA fragments from other DNA fragments of different sizes, Huber et al. in no way suggests that overloading the column is desirable for any purpose, let alone suitable for obtaining consistent amounts of DNA. In fact, Huber et al. teaches that, while constant peak half-widths were obtained with sample loads of up to 0.5 μg, at sample higher loads, peak half-widths increased with increasing sample loads. Although Huber et al. states that, "for semipreparative purposes at least 5 μg can be applied", there is no teaching that such conditions would result in isolation of defined and consistent amounts of DNA between multiple samples having DNA in excess of the binding capacity.

The Examiner concluded that "it would have been prima facie obvious for one of ordinary skill in the art to measure the DNA binding capacity of the porous and poreless boro/alumino/zirconio-silicate-borosilicate magnetic particles of Kleiber et al. using the method reported by of Huber et al." Applicants submit that the presently claimed invention is not directed to a method of measuring the DNA binding capacity of any particular material, let alone that of the porous and poreless boro/alumino/zirconio-silicate-borosilicate magnetic particles of Kleiber et al., whether by the method of Huber et al. or by any other method. Furthermore, Huber et al. is concerned with improved chromatographic separation of small DNA fragments (i.e., fragments of less than 500 base pairs) using non-porous poly(styrene-divinylbenzene) particles alkylated with octadecyl groups, which allows resolution of fragments differing by as

little as 1-5% in length. In contrast, as one of skill in the art would appreciate, the methods described in Kleiber et al. are intended to bind total DNA, not to fractionate DNA according to size. Nothing in the art of record or in the knowledge of one of skill in the art would suggest that the particles of Kleiber et al. would be suitable for use in the method of Huber et al., or that the method of Huber et al. could be used to determine the binding capacity of the particles of Kleiber et al. In fact, Huber teaches that the use of non-porous poly(styrene-divinylbenzene) particles alkylated with octadecyl groups afforded increased resolution of small DNA fragments over that obtained with, for example, even very closely related non-alkylated poly(styrene-divinylbenzene particles (see Huber et al., p. 1063, column 1, third paragraph).

The Examiner, pointing to Fig. 1A of Vogelstein as illustrating the contrast in the DNA binding capacity of various types of silica containing materials, further concluded that evidence provided by Vogelstein et al. indicates the need for discerning the DNA binding capacity of various types of silica containing materials. Vogelstein discloses that different types of glass bind to DNA differently, with respect to the mass of DNA bound, the binding kinetics, percentage of DNA bound, and recovery of DNA from the glass (Vogelstein p. 616, second column first full paragraph). However, Vogelstein is concerned with recovering high yields of DNA (see abstract and p. 616, second column first full paragraph). Vogelstein does not teach obtaining recovery of a defined and consistent amount of DNA from multiples samples according to the present invention.

One of skill in the art would understand from the claims and the specification that the claimed invention pertains to isolation of a uniform amount of DNA from multiple samples. The claims have been amended to clarify that the claimed method involves selecting the defined amount of DNA to be isolated and choosing a discrete amount of silica-containing solid support necessary to isolate the defined amount of DNA. A particular discrete amount of silica-containing solid support is contacted with each of multiple samples having DNA in excess of the binding capacity of the silica-containing solid support to obtain a defined and consistent amount of DNA from each sample.

The importance of being able to isolate defined and consistent amounts of DNA from multiple samples is discussed throughout the specification in the context of performing downstream applications. For example, at page 3, lines 1-21 of the specification, the problems of excess DNA template in amplification reactions are discussed. Traditionally, these problems

were addressed by measuring DNA concentrations prior to use in downstream applications. However, measuring DNA concentrations consumes the DNA sample and is inaccurate for samples having low concentrations of DNA (page 4, lines 16-18).

As discussed throughout the specification, the ability to isolate a consistent amount of DNA from a sample permits the DNA thus isolated to be used directly in subsequent applications requiring DNA within a particular range without first having to measure the concentration of DNA in order to determine the volume of purified DNA necessary to give an amount of DNA within a suitable range (page 5, lines 20-33; page 9, lines 10-33). This is particularly important when isolating DNA from relatively scarce sources, such as trace evidence. Applicants emphasize that while DNA isolated by the methods of the invention is suitable for use in downstream applications without further analysis or processing, the claims do not preclude the possibility of measuring the DNA concentrations. In fact, there are certain applications in which verification of DNA concentration may be required for legal purposes.

In the Bitner Declaration, Dr. Bitner discusses the importance of being able to isolate a defined and consistent amount of DNA from multiple samples in order to simplify processing, to reduce the time required to process samples, and to increase sample throughput (Bitner Declaration, paragraph 7). Because DNA samples prepared using the method of the invention contain a select defined and consistent amount of DNA, the isolated DNA can be used directly in downstream applications requiring an amount of DNA within a particular range. This represents a departure from prior art methods of isolating DNA, which emphasize maximized DNA yield (Bitner Declaration, paragraph 6).

The ability to isolate defined and consistent amounts of DNA from multiple samples addresses a long-felt need. As Dr. Bitner attests, the importance of increased sample throughput in isolating DNA cannot be overstated. For example, because prior art DNA isolation methods are very labor-intensive, there existed a backlog of several hundred thousand samples from rape victims when this application was filed in 1999 (Bitner Declaration, paragraph 8).

At paragraph 9 and 10 of the Bitner Declaration, Dr. Bitner refers to an article entitled "Robotic Extraction of Mock Sexual Assault Samples using Biomek® 2000 and the DNA-IQ™ System", authored by Susan Greenspoon and Jeff Ban of the Virginia Division of Forensic Science, which appeared in the February 2000 issue of Profiles in DNA (Exhibit B). Dr. Bitner indicated that Greenspoon and Ban describe how the DNA IQ™ System, used in conjunction

with the Biomek® 2000 robotics system, isolated uniform amounts of DNA from mock sexual assault samples containing widely varying amounts of DNA that could be used directly in a DNA amplification reaction (Bitner Declaration, paragraphs 9 and 10. The DNA IQ™ System is the term that Promega uses with customers in referring to methods of isolating a defined and consistent amount of DNA from multiple samples (Bitner Declaration, paragraph 5).

Dr. Bitner notes that experts in the field of DNA isolation have recognized the importance of the instant invention for isolating DNA for use in molecular biological methods such as amplification for genetic identity (Bitner Declaration, paragraph 11).

Dr. Weimin Sun, Scientific Director in the Molecular Genetics Department of Quest Diagnostics Nichols Institute, San Juan Capistrano, CA, evaluated the DNA IQ™ System for use in clinical samples and found that the methods yielded consistent quantities of DNA despite significant variations in the starting material, which afforded satisfactory performance in downstream applications. (See Bitner Declaration at paragraph 12 and correspondence from Dr. Sun to Mr. David Phelps, Exhibit C).

At paragraph 13 of his declaration, Dr. Bitner refers to correspondence from Kim Gorman, then President of Paternity Testing Corporation, Columbia, MO, who reported that the DNA IQ™ System was used to extract DNA from buccal swabs in a 96 well format. (See Exhibit D). Ms. Gorman noted that buccal swabs vary greatly in DNA content, and also noted that DNA multiplexes (amplification of multiple DNA loci in a single reaction) are concentration sensitive. Despite these challenges, Ms. Gorman further noted that there was no need to quantify the DNA prepared using the DNA IQ extraction method prior to use in a multiplex reaction. Ms. Gorman reported that, using the DNA IQ™ System, the total time required to process 96 samples was reduced from 6 or 7 hours using their traditional extraction method to about 3 hours, and hands on time by analysts was reduced from more than 4 hours to less than 30 minutes.

Additionally, Dr. Bitner refers to correspondence from Jeffrey Ban, Section Chief of Forensic Biology at the Virginia Department of Criminal Justice Services, Division of Forensic Science (Bitner Declaration, paragraph 14; Exhibit E). Mr. Ban reported that, using the DNA IQ™ System in conjunction with Beckman Coulter Biomek® 2000 Workstation or other similar instrumentation, could greatly increase a laboratory's throughput capabilities, thus permitting the forensic DNA community to provide better service to law enforcement agencies (Exhibit E).

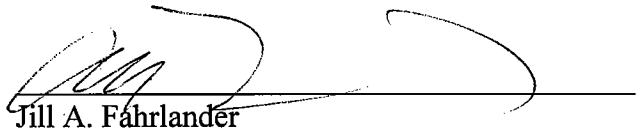
In addition, Dr. Bitner reports that Promega has been contacted by numerous law enforcement agencies that ultimately used the DNA IQ™ System to analyze forensic samples from crime scenes. For example, the Royal Canadian Mounted Police requested assistance in processing samples collected from a hog farm in British Columbia, where the partial remains of at least 26 murder victims were found. The DNA IQ™ System was also used to isolate DNA for genetic identity testing of victims at Ground Zero and human remains found in mass graves in Bosnia (Bitner Declaration, paragraph 15).

Finally, as Dr. Bitner describes at paragraph 16 of the Bitner Declaration, in 2002, Promega received an R&D 100 Award for its DNA IQ™ System. The prestigious R&D 100 Awards are given to recognize organizations for the most technologically significant products introduced into the marketplace (Bitner Declaration, paragraph 16).

In light of the foregoing, Applicants submit that the claims are in condition for allowance, and respectfully request notification to that effect. Should the Examiner feel that anything warrants further discussion, the Examiner is encouraged to contact the undersigned at the phone number below.

Please charge Deposit Account No. 50-0842 with any fees owed in connection with this submission.

Respectfully submitted,



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Docket No.: 016026-9043-US01

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